Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/IN05/000071

International filing date: 04 March 2005 (04.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: IN
Number: 626/MUM/2004
Filing date: 04 June 2004 (04.06.2004)

Date of receipt at the International Bureau: 16 August 2005 (16.08.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

PCT / IN 05 / 00071

बौध्दिक सम्पदा भारत
INTELLECTUAL
PROPERTY **INDIA**
एकस्व /अभिकल्प /व्यापार चिन्ह /
भौगोलिक संकेत
PATENTS / DESIGNS /
TRADEMARKS /
GEOGRAPHICAL INDICATIONS

सत्यमेव जयते
भारत सरकार /GOVERNMENT OF INDIA
पेटेन्ट कार्यालय /THE PATENT OFFICE
तोडी इस्टेट, 3 री मंजिल, सन मिल कंपाउंड, लोअर परेल (प.), मुंबई - 13
Todi Estate, 3rd Floor, Sun Mill Compound
Lower Parel (West), Mumbai – 400 013

दूरभाष Tel ☎ 022-2492 4058
022-2492 5092
022-2496 1370
022-24949845
022-24922710
फॅक्स Fax 🖷 022-2495 0622
022-24903852
Email patmum@vsnl.net
Website www. ipindia.nic.in

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Application and Provisional Specification as filed in this office on 04/06/2004 in respect of Patent Application No.626/MUM/2004 of **(a) M/S. IPCA LABORATORIES LIMITED, (b) 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India (c) Indian company incorporated under the Companies Act 1956.**

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 11th day of July 2005.

(A.T. PATRE)
ASSTT. CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

[See section 5(2), 7, 54 and 135; rule 39]

1. We,

   (a) **M/S. IPCA LABORATORIES LIMITED**

   (b) **48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India**

   (c) **Indian company incorporated under the Companies Act 1956**

ORIGINAL

2. Hereby declare –

   (a) that we are in possession of an invention titled **"An industrially feasible process for manufacture of crystalline Forms of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno [3,2-C] pyridine-5-acetate hydrogen sulphate salt"**

   (b) that the Provisional Specification relating to this invention is filed with this application.

   (c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventor(s) for the said invention are

   (a) **Kumar, Ashok**

   (b) A4/203 - 4, Sterling CHS,
   Sundaravan Complex,
   Andheri (West)
   Mumbai - 400 053
   Maharashtra, India

   (c) Indian National

8471

626

626/MUM/2004

4/6/2004

626 | मुंबई | 2004
MUMBAI

4 JUN 2004

Received Rs. 3000/- in Cash.
Dated 4/6/04
Vide Letter No. 8471 of the
Registrar of Patents, Mumbai.
4-6-04

(a) **Bhayani, Priti Jayesh**
(b) 8/New Krishnakunj Society,
Opp. Samrudhi Shopping Centre,
Swami Samarth Marg,
Kandivli Village, Kandivli (West)
Mumbai 400 067
Maharashtra, India
(c) Indian National

(a) **Nandavadekar, Sanjay**
(b) Kanchan Gouri Co.Hsg. Society,
Room No.19, Sector-2,
Charkope, Kandivli (West),
Mumbai – 400 067
Maharashtra, India
(c) Indian National

(a) **Burudkar, Sandip Madhavrao**
(b) Survey No.17/A, Harinagar,
Ramwadi,
Pune – 411 014,
Maharashtra, India
(c) Indian National

4. That we are the assignee(s) of the true and first inventors.

5. That our address for service in India is as follows:

GOPAKUMAR NAIR ASSOCIATES, NAIR BAUG, AKURLI ROAD, KANDIVLI (EAST), MUMBAI – 400 101.

6. Following declaration was given by the inventor(s) :

We the true and first inventors for this invention in the convention country declare that the applicant(s) herein are our assignee

(Kumar Ashok)

(Bhayani, Priti Jayesh)

(Nandavadekar, Sanjay)

(Burudkar, Sandip Madhavrao)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Following are the attachment with the application:
   (a) Provisional specification (2 copies)
   (b) Statement and Undertaking on Form 3
   (c) Form 26 (Original power of attorney in our favour has been submitted with application no. 150/MUM/2003)
   (d) Fee Rs.3000/- in cheque bearing No. 693800 dated 4th June, 2004 on Global Trust Bank Limited, Mumbai.

We request that a patent may be granted to us for the said invention.

Dated this 4th Day of June, 2004

for GNN -

Dr. Gopakumar G. Nair
Agent for the Applicant
GOPAKUMAR NAIR ASSOCIATES
Nair Baug, Akurli Road,
Kandivli (East), Mumbai – 400 101

To
The Controller of Patent
The Patent Office
At Mumbai

FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

PROVISIONAL SPECIFICATION

[See section 10, rule 13]

ORIGINAL

"An industrially feasible process for manufacture of crystalline Forms of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno [3,2-C]pyridine-5-acetate hydrogen sulphate salt."

(a) IPCA LABORATORIES LTD.

(b) 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India

(c) Indian Company incorporated under the Companies Act 1956

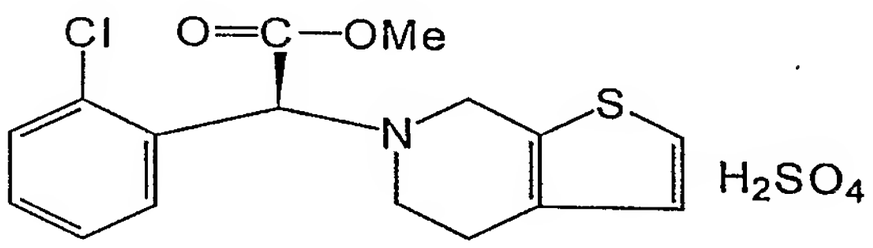
The following specification particularly describes the nature of this invention :

Technical Field:

The invention relates to an industrial process for manufacturing hydrogen sulfate salt of alpha-2-(chlorophenyl)-6,7-dihydrothieno[3,2-C] pyridine-5(4-H)-acetic acid methyl ester of Formula I, commonly known as Clopidogrel hydrogen sulphate, in its crystalline forms viz: Form-I and Form-II, in their pure forms.

Background and Prior Art :

Clopidogrel hydrogen sulfate [Formula-I, which is known as hydrogen sulfate of methyl (+)-(S)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-C]pyridine-5-acetate] is an antithrombotic agent that was disclosed in Patent EP 281459 (herein after referred as '459 patent.) in its pure enantiomeric form for the first time.



Formula – I

The '459 patent teaches the isolation of the dextro rotatory isomer of Clopidogrel by diasteriomeric salt formation of racemic base of Clopidogrel using an optically active acid such as 10-L-camphor sulfonic acid in solvents like acetone, followed by successive recrystallization of the salt until a product with constant rotatory power was obtained. The pure dextrorotatory isomer of Clopidogrel was released from the respective diasteriomeric salt by reaction with a base.

Clopidogrel was then converted into its hydrogen sulfate salt by dissolving Clopidogrel base in acetone, cooling and mixing with concentrated sulfuric acid to precipitation. The precipitate thus obtained was then isolated by filtration, washed and dried to give Clopidogrel hydrogen sulfate

in the form of white crystals whose melting point was 184°C and optical rotation was +55.1° (c = 1.891 / CH3OH). But '459 patent did not suggest any name to this polymorph of Clopidogrel hydrogen sulfate.

Subsequently International patent published application, WO 99/654915 (herein after referred as '915 patent), disclosed two polymorph forms of Clopidogrel hydrogen sulfate referred to as Form-I and Form-II. The '915 patent application identified that the precipitation method described in '459 patent had led to crystalline Form-I. The '915 also deals with a new crystalline form called Form-II of Clopidogrel hydrogen sulfate. The latter is suggested to be thermodynamically most stable crystalline form. According to '915 patent application both polymorphs, namely Form I and Form II, were prepared from the same solvent viz; acetone.

The process for obtaining crystalline Form-II of Clopidogrel hydrogen sulfate according to example 1A of the '915 patent application describes the introduction of Clopidogrel camphor sulfate in MDC and transformation of salt into the base with potassium carbonate solution. Clopidogrel base is extracted in MDC and evaporated. Residue obtained is dissolved in acetone and cooled. Addition of sulfuric acid precipitated out Clopidogrel hydrogen sulfate. Also in the same application it was described to get Form-II either by keeping mother liquor of Form-I or by heating acetone solution containing the base after addition of sulfuric acid to reflux or by subjecting the suspension to mechanical shearing using a shearing device or by inoculation.

However, this process was not suitable for the production of the Form I of Clopidogrel reproducibly on an industrial scale owing to its thermodynamic instability in solvents like acetone. This problem became the subject of the patent application WO 2004020443 (herein after referred as '443 patent application).

According to the '443 patent application, a process was claimed to produce Form I consistently by forming hydrogen sulphate salt of Clopidogrel from a solvent selected from the series of C_1-C_5 alcohols or their esters with C_1-C_4 acids, optionally of mixture of alcohols and esters. The process involves dissolving Clopidogrel base in solvents like isopropyl alcohol and/or butyl

acetate, cooling the mixture, adding sulfuric acid and inoculating the mixture with Form-I of Clopidogrel hydrogen sulfate. Stirring the crystallized mixture precisely at a temperature between –5°C and 15°C to get crystals of Clopidogrel in Form-I. In another process variant, the subject of '443 patent application, the Clopidogrel hydrogen sulphate was directly dissolved at reflux in the above mentioned solvents and crystallized under cooling.

Although the process mentioned in the '443 patent application works in butyl acetate, it fails to give pure Form I in other solvents like ethyl acetate under the specified conditions. As the Form I is thermodynamically unstable, the process variant of bringing the salt solution to a higher temperature resulted in Form II or its mixture with Form I.

This finding is in agreement with the prior art disclosed in United States patent application 2003/0225129 A_2 (herein after referred as '129 patent application), where isopropanol was used to produce Form-IV crystals by a process comprising the steps of preparing solution of Clopidogrel hydrogen sulfate either by using Clopidogrel base or its hydrogen sulfate salt in isopropanol at reflux and cooling to precipitating Clopidogrel hydrogen sulfate and separating the mentioned polymorph, i.e. Form IV.

The '129 patent application also describes a process for the preparation of Form-II from solvents selected from dichloromethane, 1,4-dioxane, toluene, chloroform, ethyl acetate, methyl ethyl ketone and t-butyl methyl ether. The '129 patent application, for the first time, claimed to produce Form II from ethyl acetate which was the main subject of '443 patent application.
It is clear from above mentioned embodiments that same solvent gives two different crystalline forms under different experimental conditions.

So, it is evident from the prior art that methods to produce Form-I of Clopidogrel hydrogen sulphate from different solvents are poorly reproducible, necessitating the optimization of experimental conditions apart from the selection of solvents. Since Form-I and Form-II are thermodynamically controlled forms; they require very specific temperature range and specific conditions for getting reproducible results. Also, a minor variation in condition appears to give

Form-II instead of expected Form-I or a mixture of Form-I & Form-II. Since Form I of Clopidogrel hydrogen sulphate is required for pharmaceutical formulation, the importance of a rugged method which gives Form I consistently doesn't require any emphasis.

Apart from the inconsistency of the process in solvents like ethyl acetate, the process given in the '443 patent application suffers from problems from an industrial scale-up point of view.

1) This process uses lower temperature for the salt formation in which case the product forms a lumpy mass which sticks to the stirrers and makes it difficult to disperse.
2) The workable conditions are by varying precisely the temperature at different set points which is difficult in large batches, since the mass is difficult to disperse at low temperature.
3) The workability of the process found to limits to few solvents mainly butyl acetate and isopropyl alcohol.

Thus there is a need to get industrially reliable process for the preparation of Form-I and Form-II without the contamination of one into other Form. So it was of interest to find a specific solvent where the crystallization can be performed at a temperature near to ambient temperature yielding Clopidogrel Form I in its pure state. Also of interest to see a wide workability of high temperature to effect the crystallization fast and easy dispersibility, an important factor for operations. Another area of interest was to find the conditions, where the transformation of Form I to Form II takes place in the same solvent. These objectives become the subject of the present invention.

Since Form-I and Form-II and other forms of Clopidogrel are thermodynamically controlled, it is not only the solvent dependent but specific experimental condition and temperatures with skill of art to reproduce the form-I, Form-II and other polymorphs.

Summary of invention :

The present invention provides an industrial manufacturing process for preparing compound of Formula (I) in ethyl acetate, in its crystalline Form-I in a reproducible manner without detectable

contamination of Form-II at an industrially feasible temperature ranging from 18° to 30°C in time range of 8 to 10 hours. The present invention also provides process for the formation of Clopidogrel Form II from ethyl acetate at a temperature of 45°C to 50°C without detectable contamination of Form I.

Further, the present invention provides an industrial process for preparation of both Form-I and Form-II from the same solvent at different experimental condition, which gives operation-wise flexibility and excellent reproducibility, making the process practical and plant friendly.

In another aspect, the present invention provides an industrial process for the preparation of Form II Clopidogrel hydrogen sulphate from a commonly used solvent viz. Isopropanol. The present invention also proves that not only the solvent but also the operational conditions are important to get different polymorphs of Clopidogrel hydrogen sulphate.

Brief description of Figures

Figure 1. represents Powder X-Ray diffraction pattern (PXRD) of clopidogrel hydrogen sulphate Form I prepared according to example 1 of the present invention.

Figure 2. represents Powder X-Ray diffraction pattern (PXRD) of clopidogrel hydrogen sulphate Form II prepared according to example 2 of the present invention.

Figure 3. represents Differential Scanning Calorimetry record of Form I of clopidogrel hydrogen sulphate prepared according to example 1 of the present invention.

Figure 4. represents Differential Scanning Calorimetry record of Form II of clopidogrel hydrogen sulphate prepared according to example 2 of the present invention.

Figure 5. represents Powder X-Ray diffraction pattern (PXRD) of clopidogrel hydrogen sulphate Form I standard as given in '915 patent.

Figure 6. represents the spectrogram obtained by Fourier Transform infra Red spectrometry (FTIR) of clopidogrel hydrogen sulphate Form I prepared according to example 1 of the present invention

Figure 7. represents the spectrogram obtained by Fourier Transform infra Red spectrometry (FTIR) of clopidogrel hydrogen sulphate Form II prepared according to example 2 of the present invention

Detailed description of the invention

This invention relates to an industrial process for the preparation of Form I and II of Clopidogrel hydrogen sulphate on large scale.

Large scale production of these two crystalline Forms according to the process described in the '915 patent resulted in a mixture or contaminated with either forms at a higher percentage. Also the improved process of '443 patent application resulted in scale-up problems on large scale due to lump formation and semisolid/sticky nature of the product at lower temperature. Also encountered precise control of temperature at different set points as stated in the '443 patent application on large scale production.

This lead us to find a suitable temperature where these problems are minimized and ensure reproducibility of Form I and II, particularly Form I. This research has led to a process where Form I and Form II can be produced reliably from a single solvent.

In one aspect, the present invention provides an industrial process for preparing polymorph Form I of Clopidogrel comprising steps of dissolving the Clopidogrel base in ethyl acetate, cooling to a temperature of 18°C, adding concentrated sulphuric acid (98%, d= 1.84) with or without maintaining temperature at 18°, raising to a temperature of 28°-30° C for a period of 7-10 hours and filtering the crystals obtained.

In the process, the temperature range of 18° – 30°C gave Form I reproducibly on a large scale. Within this temperature range an easily dispersible solid is obtained and slight imbalance of temperature is well tolerated to give Form I consistently.

In the process, the preferred concentration of sulphuric acid was in the range of 90 % - 98% and the molar ratios were in the range of 1 to 1.1 with respect to the Clopidogrel base. The most preferred concentration of sulphuric acid used in the salt formation was 96%.

In a preferred embodiment the exotherm of sulphuric acid addition is controlled by cooling and maintaining the temperature between 18°-24°C

The Form I so obtained was confirmed by PXRD, DSC and FTIR without any detectable quantity of Form II or other polymorphic Forms with respect to the standard Form obtained by the process of '915 patent.

In another aspect, Form II of Clopidogrel hydrogen sulphate is prepared from the same solvent ethyl acetate comprising steps of dissolving Clopidogrel base in the solvent, heating to a temperature of 45° C, adding concentrated sulphuric acid (96%, density = 1.83), stirring the reaction mixture at 45° C to 50° C for a period of 1 hour, cooling to 30° C and continue stirring for a period of 4 - 7 hours to effect the complete crystallization.

In the process, the preferred concentration of sulphuric acid was in the range of 90 % - 98% and the molar ratios were in the range of 1.0 to 1.1 with respect to Clopidogrel base. The most preferred concentration of sulphuric acid used in the salt formation was 96%.

The Form II obtained by the process of the invention was confirmed by PXRD, DSC and FTIR and found to be identical with it disclosed in the '915 patent without any detectable contamination of Form I.

In another embodiment, the present invention provides an industrial process for the preparation of Form II of Clopidogrel hydrogen sulphate from isopropyl alcohol comprising steps of dissolving Clopidogrel base in solvent, adding concentrated sulphuric acid at a temperature of 28° - 30° C, stirring to effect complete crystallization for a period of 12 to 15 hours, filtering and drying the crystals. The crystal form identified equivalent to Form II.

In a preferred embodiment of the process the concentrated sulphuric acid is added as a solution in isopropyl alcohol.

The following actual example further illustrates the present invention without limiting its scope.

Examples

Example 1

Clopidogrel base (5.79 kgs) was dissolved in ethyl acetate (30 liters) at room temperature. This mixture was cooled to 18° C and concentrated sulphuric acid (96%, density = 1.83) was added (1.02 liters) maintaining temperature 18° to 20° C while addition. The reaction mass was stirred for 30 minutes and warmed slowly to 28° – 30° C in 30 to 40 minutes. The formed crystals were stirred for 8 hours. The solid obtained was filtered under suction and washed with ethyl acetate and dried in oven at 48° C for 3 hours. The yield of the final solid product, Form I Clopidogrel hydrogen sulphate was 6.7 kgs (88%). (PXRD pattern incorporated :figure 1)

Example 2

Clopidogrel base (5.79 kgs) was dissolved in ethyl acetate (30 liters) at room temperature. This mixture was heated to 45° C and concentrated sulphuric acid (96%, density = 1.83) was added (1.02 liters). The reaction mass was stirred for 30 minutes at 45° to 50° C. The formed crystals were cooled to 30° C in one hour and stirred for 4 hours. The solid obtained was filtered under suction and washed with ethyl acetate, and dried in oven at 48° C for 3 hours. The solid after drying weighed 6.5 kgs (86%) and identified as pure Clopidogrel hydrogen sulphate Form II (PXRD pattern incorporated :figure 2)

Example 3

Clopidogrel base (5.79 kgs) was dissolved in ethyl acetate (30 liters) at room temperature. This mixture was cooled to 20° C and concentrated sulphuric acid (98%, density = 1.84) was added (1.02 liters). The temperature rose to 28° C while addition and the reaction mass was stirred for

10 hours at 28° – 30° C. The solid obtained was filtered under suction and washed with ethyl acetate and dried in oven at 48° C for 3 hours. The solid after drying weighed 6.8 kgs (89.6%) and was identified as pure Clopidogrel hydrogen sulphate Form I (PXRD pattern incorporated as in example 1)

Example 4

Clopidogrel base (7.25 kgs) was dissolved in isopropyl alcohol (62.5 liters) at room temperature. This mixture was maintained at 28° to 30° C and concentrated sulphuric acid solution in isopropyl alcohol (prepared by mixing 1.14 liters concentrated sulphuric acid and 43.5 liters isopropyl alcohol) was added. The reaction mass was stirred for 12 hours at 28° to 30° C. The solid obtained was filtered under suction and washed with ethyl acetate, and dried in oven at 48° C for 3 hours. The solid after drying weighed 7.6kgs (80%) and was identified as pure Clopidogrel hydrogen sulphate Form II (PXRD pattern as in example 2).

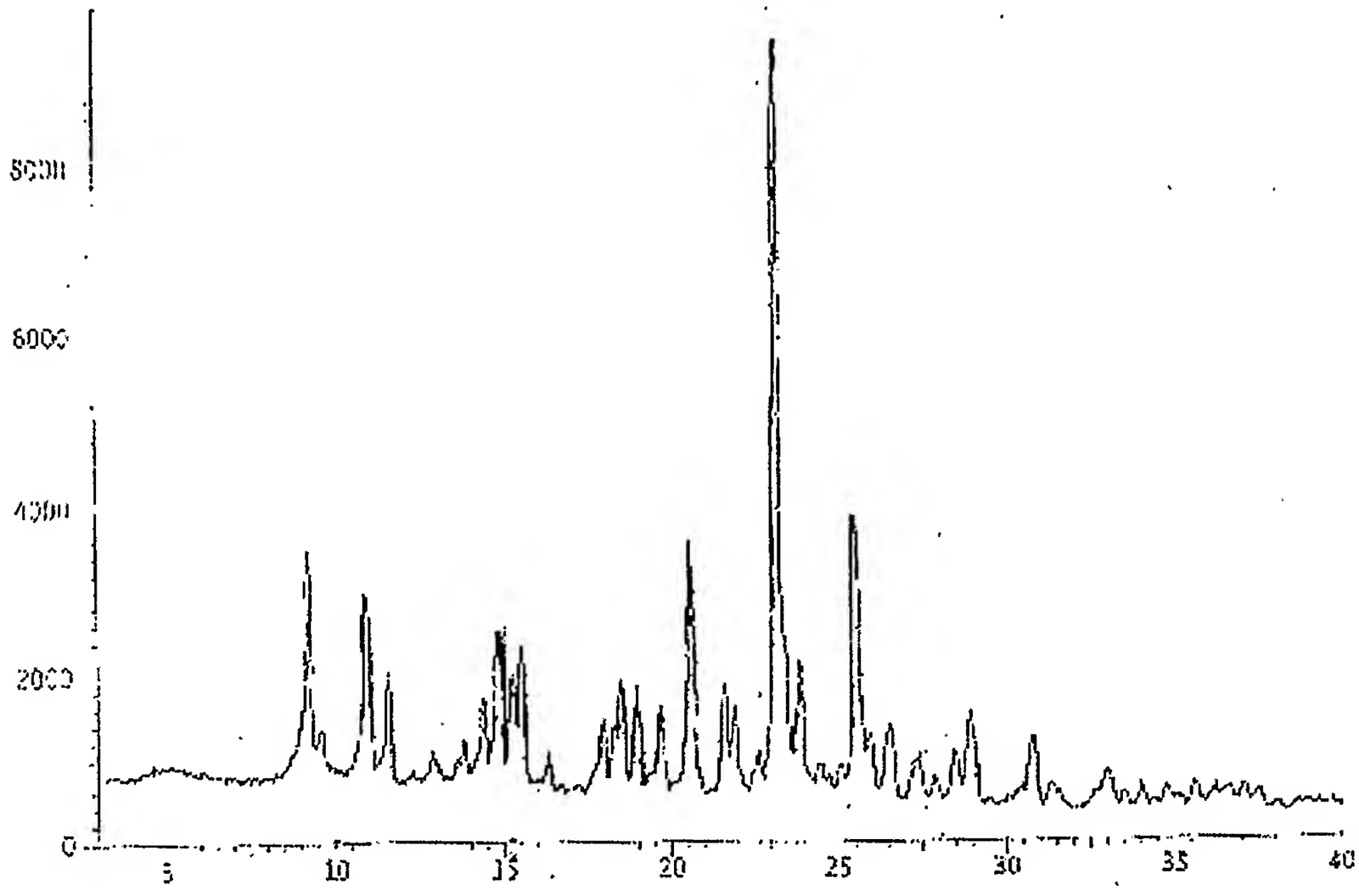
Dated this 4th day of June 2004

Dr. Gopakumar G. Nair

Agent for Applicant

Applicant : IPCA Laboratories Ltd.
Application No. : /MUM/2004

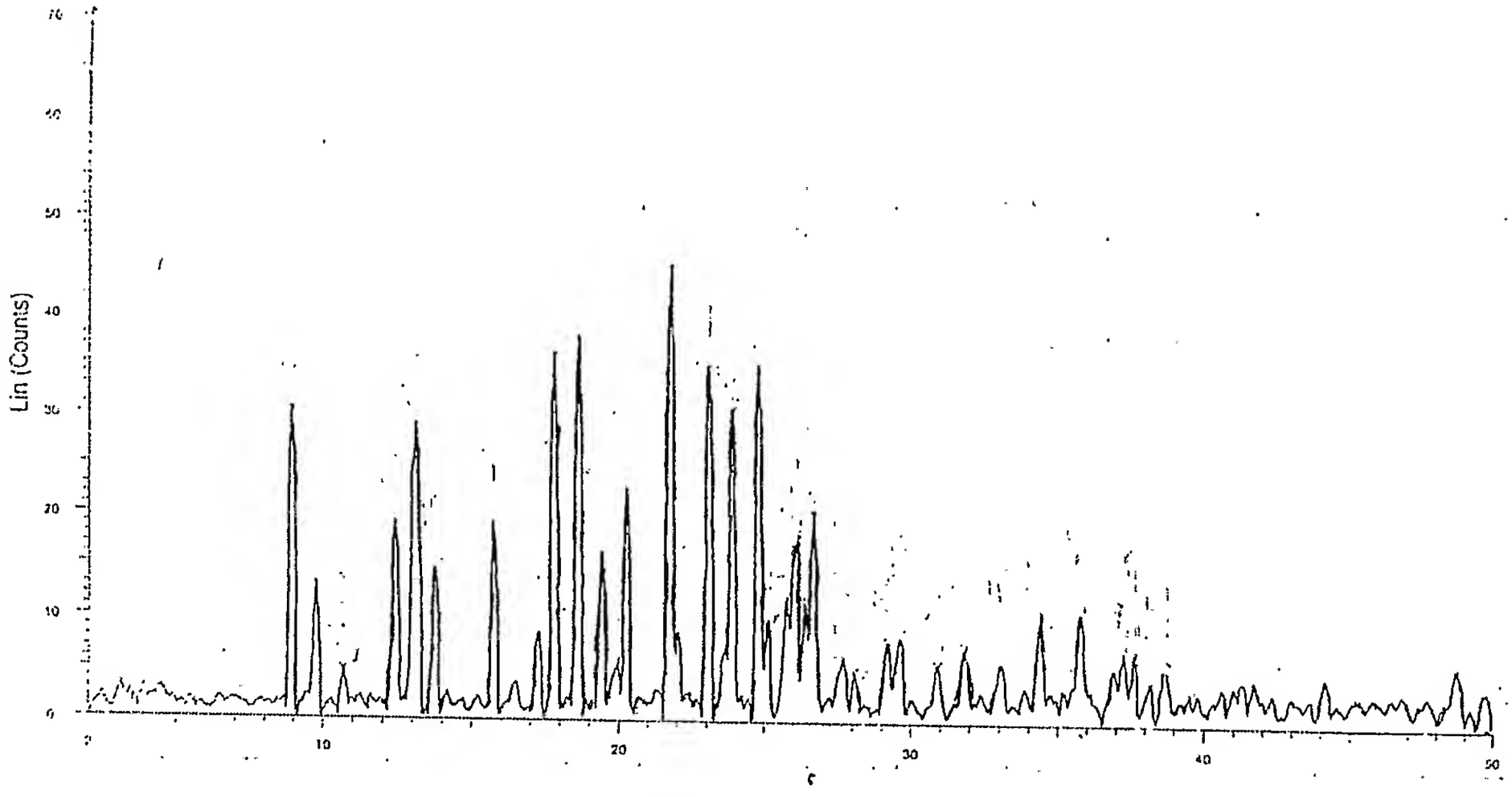
Total No. of Sheets 7
Sheet No. 1



for IPCA -

Dr. Gopakumar G. Nair
Agent for Applicant

4 JUN 2004



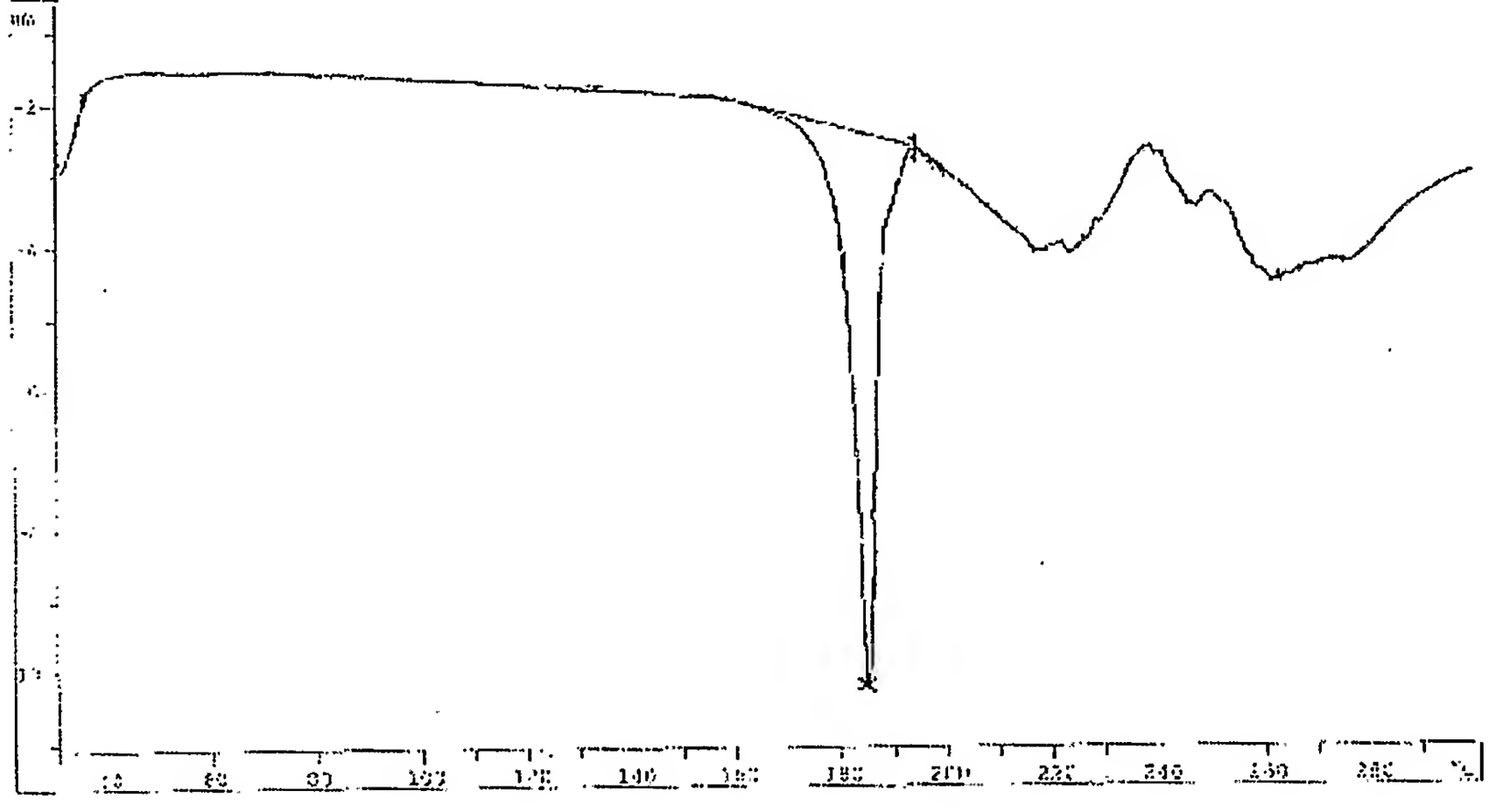
for IPCA

Dr. Gopakumar G. Nair
Agent for Applicant

Applicant : IPCA Laboratories Ltd.
Application No. : /MUM/2004

Total No. of Sheets 7
Sheet No. 3

^cxo



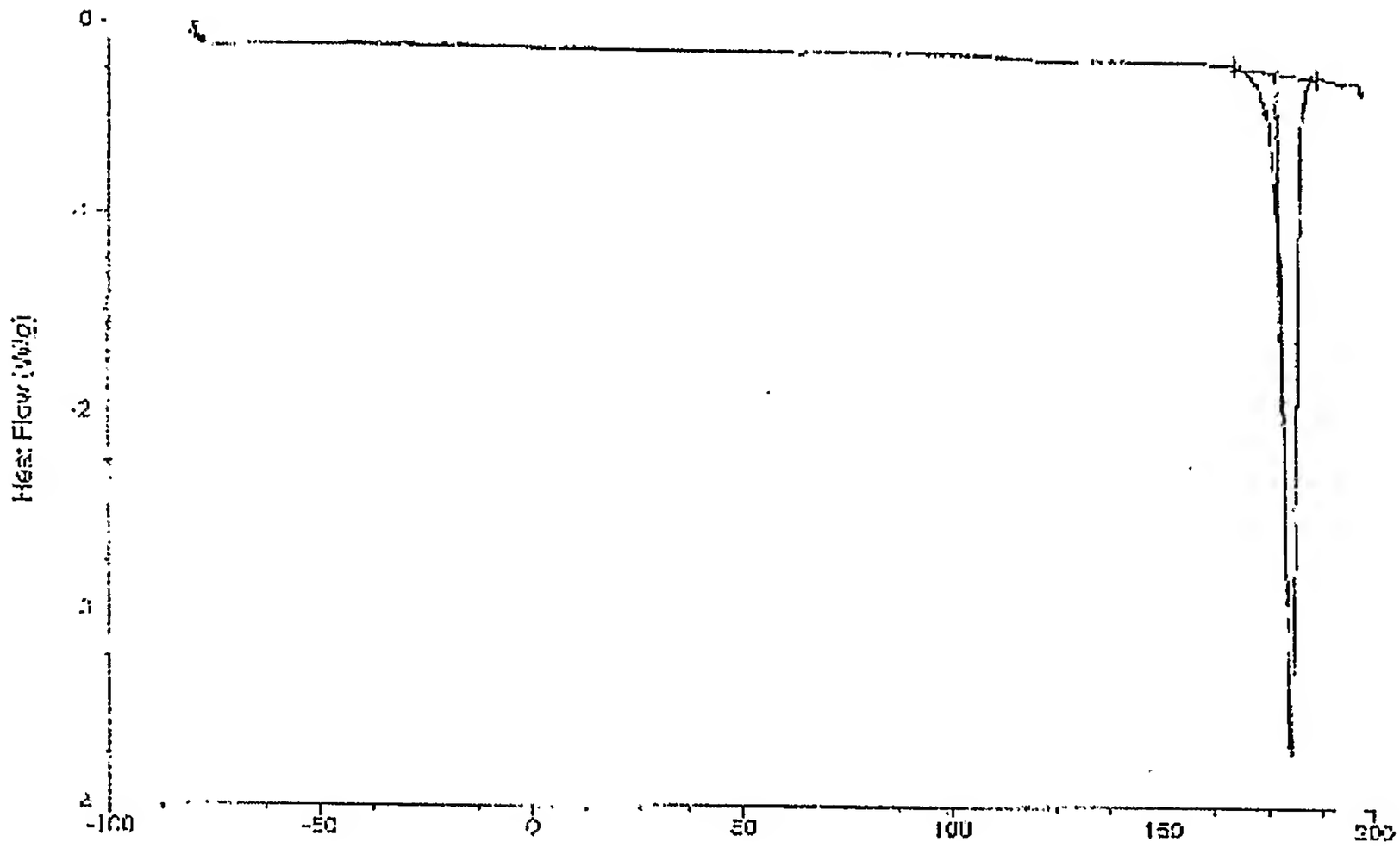
for Sm4 -

Dr. Gopakumar G. Nair
Agent for Applicant

4 JUN 2004

Applicant : IPCA Laboratories Ltd.
Application No. : /MUM/2004

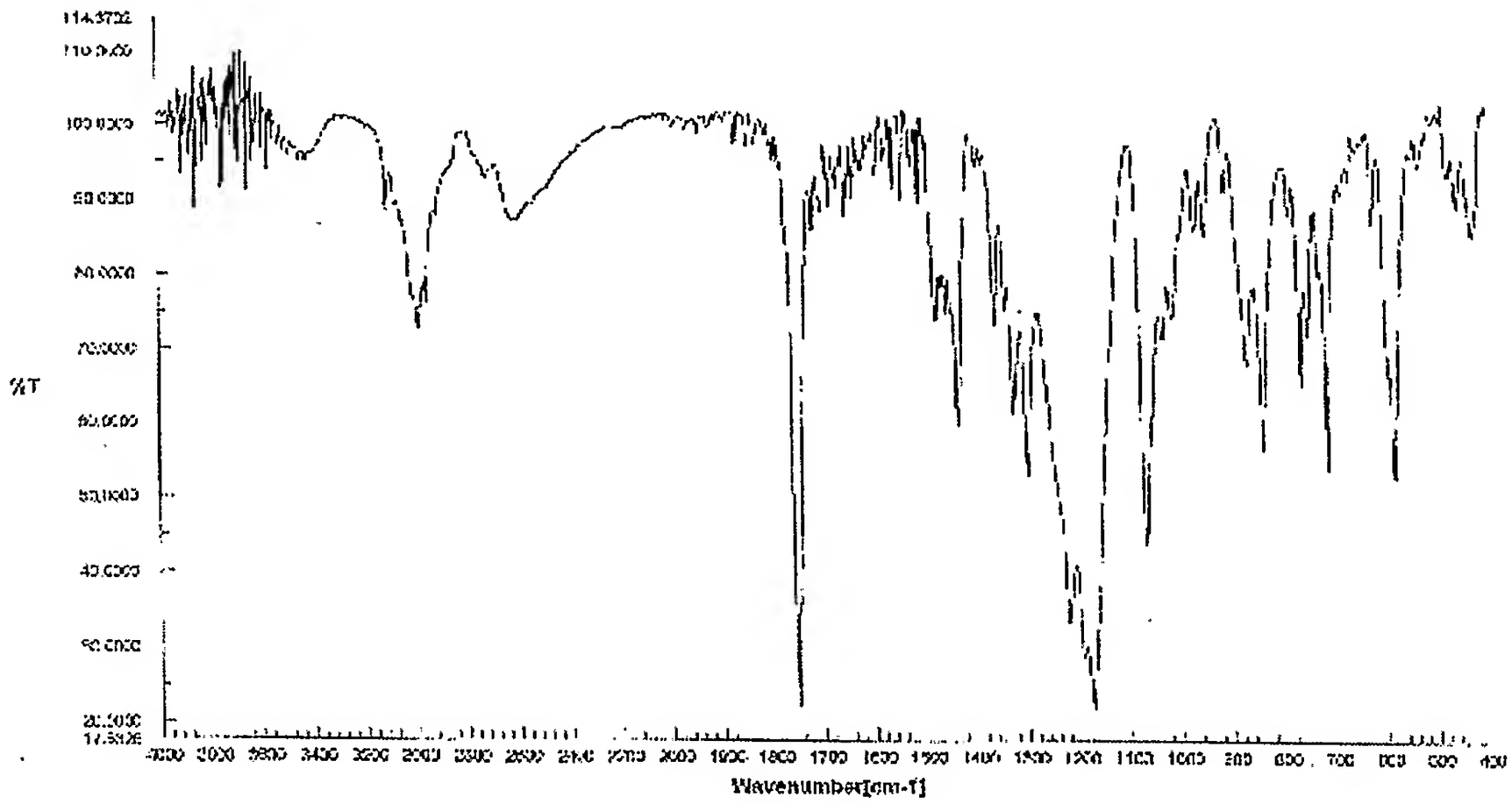
Total No. of Sheets 7
Sheet No. 4



for Smt-

Dr. Gopakumar G. Nair
Agent for Applicant

4 JUN 2004



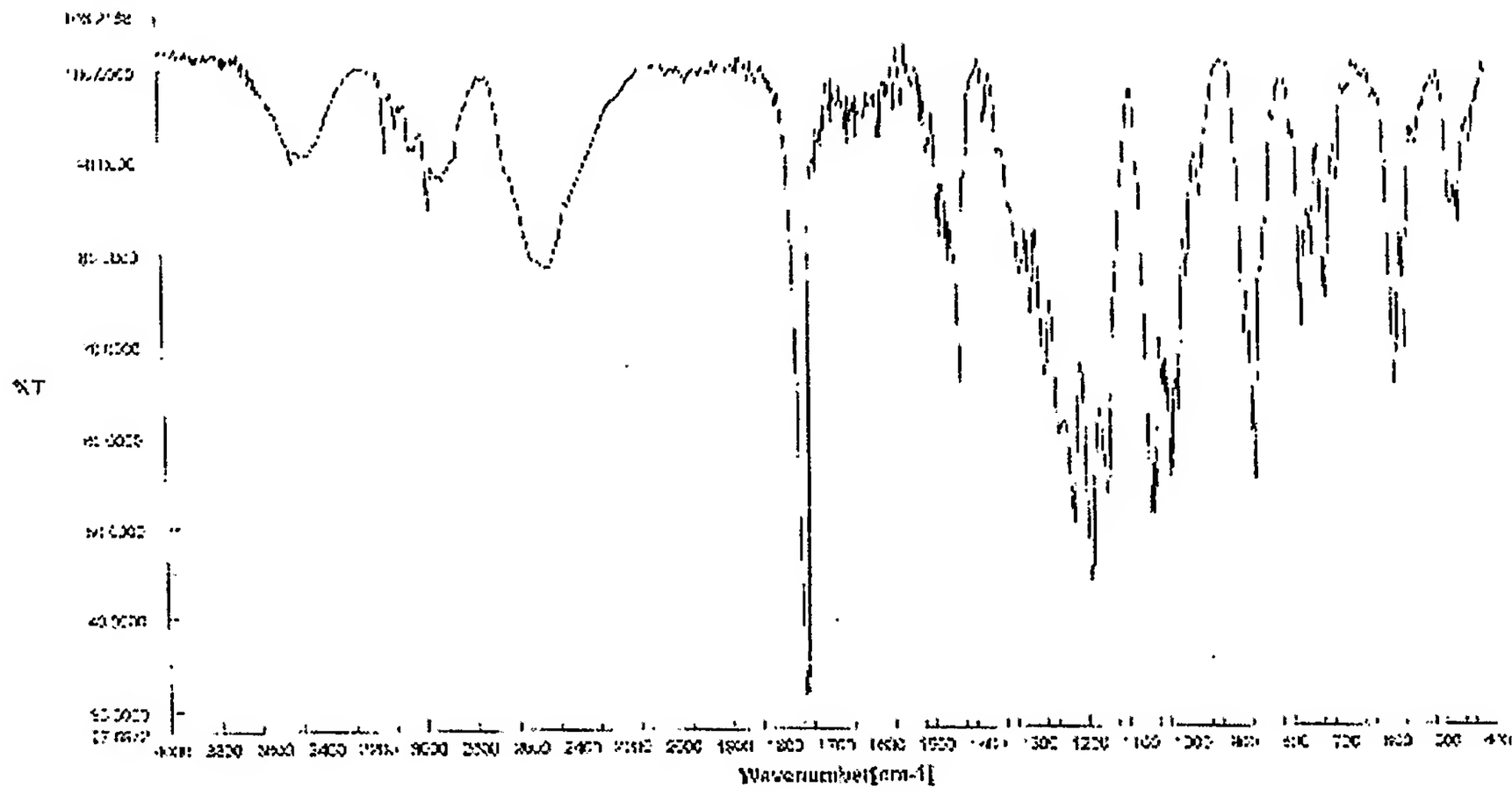
for Sml—

Dr. Gopakumar G. Nair
Agent for Applicant

4 JUN 2004

Applicant : IPCA Laboratories Ltd.
Application No. : /MUM/2004

Total No. of Sheet 7
Sheet No. 7



for Gopa

Dr. Gopakumar G. Nair
Agent for Applicant

4 JUN 2004